

Delayed Reactions Following Penicillin Therapy*

PRELIMINARY REPORT

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AS penicillin has become more widely used, reports dealing with reactions occurring during its administration have appeared with increasing frequency.^{1,2,5,6,7,8,9} However, examination of literature has failed to reveal any detailed account of delayed reactions occurring after cessation of penicillin therapy.

It is the purpose of this report to describe seven cases in which reactions, varying in severity from mild to extremely severe, appeared at intervals of two to twenty-eight days after the last administered dose of penicillin.

REPORT OF CASES

CASE 1: A 49-year-old white male entered the hospital for penicillin therapy of latent syphilis. He had been known to have a positive Wassermann for the past 19 or 20 years, but he gave no history of primary or secondary lues. He had had sporadic mapharsen and bismuth therapy during the last five to six years, and both drugs had caused typical skin reactions. No history of asthma, hay fever or urticaria was obtained. Other than the positive Wassermann and Kahn tests, there were no other important physical or laboratory findings. Spinal fluid Wassermann test was negative.

He was given 3,000,000 units of sodium penicillin in divided doses intramuscularly over a period of seven days and was then discharged. His course remained uneventful until three days after the last injection of penicillin, at which time he re-entered the hospital because of intensely pruritic giant hives over the entire body. Symptomatic therapy with calamine lotion, calcium gluconate intravenously, ephedrine orally, and epinephrine intramuscularly gave the patient little relief. He became edematous over the entire body including head, palms and soles. By the third day, a gnawing epigastric pain appeared accompanied by nausea and vomiting. These gastrointestinal symptoms were promptly controlled by milk and alkaline water. The temperature went up as high as 40° C. The following day he complained of severe headache and neck stiffness, and became delirious. Urinalysis at the onset of this reaction contained one plus albumin but was otherwise normal. There was a slight leukocytosis of 12,000 with 90 per cent polys and no eosinophiles. Edema and urticaria slowly subsided and the patient became asymptomatic ten days after the onset of the reaction.

CASE 2: An 85-year-old white male with generalized arteriosclerosis and hypertension entered the hospital because of a septic sore throat. Physical examination revealed a moderately severe acute pharyngitis. On entry the white blood cell count was 10,000 with 74 per cent polys, 17 of which were stab cells. He was given 25,000 units of penicillin every three hours, and after two days of therapy a scarlatiniform eruption appeared over the

entire chest and abdomen. Penicillin treatment was continued for three more days in spite of the eruption, but was abandoned because of intense pruritus. A total of 1,295,000 units had been given. The patient was discharged three days later after the eruption and urticaria had completely subsided.

Four days after discharge the patient developed giant ecchymoses over the entire body. These were most pronounced over the injection sites on the buttocks and were also accompanied by intense pruritus. There was no leukocytosis, nor any reduction of hemoglobin or platelet count. Treatment was symptomatic and convalescence required three weeks.

CASE 3: A 50-year-old white male entered the hospital because of a low back injury with nerve root irritation in the lumbar region. A limited fusion of the lumbosacral area was performed and subsequently a superficial wound infection due to staphylococcus aureus developed. Healing was obtained after about 1,000,000 units of combined local and intramuscular penicillin, and he was discharged one and a half months after entry.

Approximately ten months later, a draining sinus developed in the central portion of the lumbar wound, and he was re-hospitalized. The old scar was excised, the tract traced down to a silk suture in the superficial fascia, and 20,000 units of penicillin was placed in the wound before closure. The patient was also given 15,000 units of penicillin intramuscularly every three hours for seven days, then decreased to 5,000 units every three hours for another day. He was discharged on the 19th hospital day.

The patient returned to the hospital four days after discharge, stating that giant hives had developed two days after cessation of penicillin therapy. On examination, advanced urticarial lesions were found over the body, scalp and extremities, and the hands and feet were markedly edematous. Urinalysis and blood count were normal. The patient died on the fourth hospital day of toxemia from a gas bacillus infection which developed 36 hours before death. The source of the infection was not determined.

CASE 4: A 30-year-old white male received 1,000,000 units of penicillin orally given every three hours for one week, for a chronic rectal fistula. Two days after cessation of therapy, giant hives appeared over both palms and then over the thorax and extremities. Markedly painful edema of both soles appeared and he was unable to walk. Temperature rose to 39.4° C. accompanied by dyspnea and palpitation. This reaction was moderately severe, but he was able to remain at home and recovered in two weeks with symptomatic therapy.

This patient gave no history of previous asthma, hives or eczema. He had received 15 injections of penicillin (dosage unknown) one year before with no untoward effects.

CASE 5: A 44-year-old white female was hospitalized because of a severe pruritus vulvae and ani. A total of

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540,000 units of sodium penicillin was given in 30,000 unit doses every three hours.

Twenty-eight days after the last penicillin injection, the patient had a sudden onset of severe pruritus and urticaria about the neck; these rapidly spread to the chest, abdomen, and extremities. There was also a severe "vice-like" headache, low mid-abdominal pain, and dysuria. She could not walk because of pain and swelling of the feet. During the first three days of the reaction the temperature ranged from 38.8° to 39.4° C. and complete recovery required two weeks.

This patient gave no history of allergic manifestations or previous penicillin therapy.

CASE 6: A 30-year-old white female was hospitalized for menorrhagia of two months' duration. A left salpingo-oophorectomy was performed because of tubal pregnancy. During the operation 500 cc. of whole citrated blood was given. On the eighth post-operative day she developed a left femoral phlebitis for which she was first given sulfadiazine without improvement, and then 2,760,000 units of penicillin intramuscularly over an 11-day period. Recovery followed and the patient was sent home on the 31st post-operative day. Seven days after penicillin therapy had been discontinued, she developed giant urticaria of the face, hands, arms, thighs, and back, with moderately severe pruritus. She was given ephedrine orally, and in four days she was asymptomatic. This reaction was comparatively mild. There had been no previous penicillin treatment but there was a history of asthma from infancy to the age of 14, with no allergic manifestations for the last 16 years.

CASE 7: A 29-year-old white male had been in good general health with no past personal or family history of allergy, urticaria, or arthritis. Sodium penicillin, in a total dosage of 400,000 units given intramuscularly every three hours over a three-day period, was instituted for a moderately severe purulent bronchitis accompanying an influenza-like infection. Prompt drop in fever from 38.8° C. to normal with clearing of purulent sputum occurred on the last day of therapy.

The patient rapidly became asymptomatic and remained so until nine days after the last dose of penicillin, when an abrupt onset of marked redness, tenderness, swelling and pain in the soft tissues about both wrists and the small joints of both hands was noted. Twenty-four hours later diffuse, intensely pruritic, giant urticarial wheals appeared over most of the body. Joint involvement then spread to both knees and shoulders, and tender 3x3 cm. deep subcutaneous nodules appeared adjacent to these joints. Mild hydrarthrosis of the left knee followed. The soles of both feet, and both dorsa and palms of the hands, became hot, painfully edematous, and redness, and edema of the eyelids and posterior pharynx ensued. The temperature rose to 38.8° C., and the patient became quite incapacitated. There was a leukocytosis of 14,200, with a normal differential count, and the urinalysis was normal.

No relief was obtained from the usual measures, including oral ephedrine and amytal, multiple injections of 1:1000 epinephrine, and intravenous calcium gluconate. "Benadryl," 50 mgm. twice daily (oral), produced relief from pruritus but had no effect upon edema or joint pain.

Slow subsidence of joint swelling, redness, and tenderness with gradual disappearance of nodules and urticaria occurred. All signs and symptoms had completely disappeared ten days after the onset of the reaction.

COMMENT

As can be seen in the accompanying table, reactions were unrelated to the duration or quantity

of penicillin, and occurred after oral as well as after intramuscular administration. The one case

Case	Total Units Penicillin	Route of Administ.	Duration of Treatment	Interval between last dose and onset of reaction
1.	3,000,000	Intramusc.	7 days	3 days
2.	1,300,000	Intramusc.	5 days	7 days
3.	900,000	Intramusc.	8 days	2 days
4.	1,000,000	Oral	7 days	2 days
5.	540,000	Intramusc.	2½ days	28 days
6.	2,760,000	Intramusc.	11 days	7 days
7.	400,000	Intramusc.	3 days	9 days

which reacted after oral therapy had received parenteral penicillin one year before. One further case we are aware of developed mild but diffuse urticaria seven days following the testing of a penicillin aerosol apparatus, with inhalation of an estimated 5,000 units. Thus it is likely that this route of administration, as well as oral and intramuscular routes, is not free from delayed effects. It is significant that the majority of these patients gave no allergic histories, and did not suffer from fungous "id" reactions.^{3,4} Reactions were considered severe in six out of the seven cases, producing systemic as well as local manifestations. Systemic reactions consisted of fever, prostration, gastro-intestinal symptoms, severe headache, mild leukocytosis and albuminuria. Local reactions varied with the severity of the process and consisted of diffuse giant urticaria, intense pruritus, scarlatiniform eruption, severe arthralgia, hydrarthrosis, ecchymosis, and the formation of tender deep subcutaneous nodules resembling those seen in erythema nodosum. One or several of these local manifestations could be seen in the same patient. The general picture in two cases resembled that seen during severe serum reactions.

Studies of penicillin sensitivity occurring during therapy, or on re-administration of the drug, seem to indicate that true allergy to penicillin does occur.^{8,9,2,1,3} Why the manifestations should be so long delayed, as illustrated by this report, requires further study.

It is not our purpose at this time to discuss in detail the possible mechanisms involved in these delayed reactions. However, we consider them striking enough to warrant description. Awareness of their occurrence with the possibility of one or more weeks of incapacitation demands circumspection before penicillin is prescribed for illnesses which would otherwise run a self-limited course.

SUMMARY

1. Seven cases of delayed reactions following penicillin administration are reported.

2. Reactions included urticaria, joint involvement, ecchymoses, gastro-intestinal and central nervous system manifestations. Severity of the reaction was not related to the amount or route of administration.

3. Delay in appearance of these reactions

varied from two to twenty-eight days after cessation of penicillin therapy.

4. Incapacitation resulting from the reactions averaged about two weeks.

5. Circumspection regarding use of penicillin in otherwise self-limited illnesses, and its reservation for use only in disease processes with well defined indications, is urged.

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DOCTORS REPORT TWO CASES OF RARE DISEASE CARRIED BY RATS

A new complication of a heretofore rare rat-borne disease, the first of its kind to be recognized in the United States, is reported in the August 17 issue of *The Journal of the American Medical Association* by three Rochester, N. Y., physicians.

They state that they treated two patients suffering from a kidney infection caused by leptospiral organisms which are carried by rats. This infection usually affects the liver.

The authors—W. W. Stiles, M.D., J. D. Goldstein, M.D., and W. S. McCann, M.D., from the Departments of Bacteriology and Medicine of the University of Rochester School of Medicine and Dentistry—state that "instances of this 'pure' renal form of leptospirosis are fairly common abroad, but prior to this report no cases have been recognized in the United States. The two patients observed in Rochester are the first confirmed instances of anicteric leptospiral nephritis to be reported in this country."

The first patient was a schoolboy, aged 17, who had symptoms of vomiting, diarrhea, headache, severe backache and a temperature of 103 F. He had been swimming almost daily in the Erie Barge Canal near Pittsford, N. Y., and although the canal was known to be infested

with rats he was not aware of any direct contact with the rodents. He was aware that water had entered the upper respiratory passages on several occasions. He was discharged from the hospital on the 19th day after the onset of his illness and remained in bed at home for an additional five weeks. The patient was treated with a high protein, salt free diet, and given a large amount of fluids.

The second patient was a dairy worker with the same general symptoms. The article points out that "for the past several years the patient had worked in a milk pasteurizing plant in Pittsford, N. Y. He said that rats were frequently seen about the plant and that approximately three weeks before this illness one of them had become caught in the mechanism of a bottle washer, and its macerated tissues had been thrown about and over him." Fever persisted until the 16th day of illness in this patient. He remained in bed two weeks at home after discharge from the hospital.

The infection was discovered in both instances after a total of 60 guinea pigs were used in testing the bloods of the patients. The guinea pigs are very susceptible to leptospira.

